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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,896	08/25/2000	Jeffrey L. Cleland	P0998D2	6985

7590 10/08/2002

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 10/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,896	CLELAND ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-34 and 37-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-34 and 37-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 6/17/02 (paper no. 8) is acknowledged and entered into the record. Claims 26,28-34,37-50 and newly added claim 51 are now pending and examined on the merits.

2. The declaration filed 6/17/02 (paper no. 9) is acknowledged.

Information Disclosure Statement

3. The Information Disclosure Statement filed 6/17/02 (paper no. 10) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections Withdrawn

4. The rejection of claims 26, 28-34, 37-50 under 35 USC 112, 1st paragraph as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art, is withdrawn in light of the persuasive arguments set forth by the applicant.

5. The rejection of claims 26,28-34, 37-50 under 35 USC 103(a) as being obvious over Valone *et al* in view of Press *et al* and Natali *et al* and further in view of Burton *et al* is withdrawn in light of the arguments presented by the applicant.

New Claim Rejections

Claim Rejections - 35 USC § 112

6. Claims 26, 28-34, 37-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer comprising the administration of rhuMAB HER2 (HERCEPTIN®), does not reasonably provide enablement for a method of treating cancer with any HER2 antibody. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are drawn to a method of treating cancer comprising the administration of a formulation comprising an antibody against HER2 receptor in a human.

The state of the prior art and the predictability or lack thereof in the art: Although the art does provide ample evidence that certain HER2 antibodies (HERCEPIN®) are effective in treating certain types of cancer, such as breast cancer, it has not taught that all HER2 antibodies are effective in treating cancers by inhibiting cell growth. One such example Stancovski *et al* (PNAS USA 1991 Oct;88(19):8691-8695) characterizes the effects of various antibodies (anti- ErbB2) that bind the extracellular domain of the HER2 receptor for their ability to inhibit tumor cells growth. Stancovski *et al* teach that while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the antibodies actually accelerated tumor cell growth (see pg 8693, col 1).

The amount of direction or guidance present and the presence or absence of working examples: The instant specification has not disclosed to one of skill in the art which antibodies are encompassed in the scope of the claims. Because the specification has not disclosed which antibodies are encompassed and because the epitope to which these unknown antibodies bind is not disclosed, one of skill in the art would not know whether the antibody or antibodies disclosed in the instant application are the same or similar to the previously described HERCEPTIN® antibody. Further, because the undisclosed antibodies encompassed by the claims of the instant application are not known and no working examples have been described which function in a capacity similar that disclosed for HERCEPTIN®, one of skill on the art would not know whether

a lyophilized formulation comprising antibody/antibodies, lyoprotectants, and bulking agents, is capable of functioning as an anti-cancer agent.

The breadth of the claims and the quantity of experimentation needed: Given the broad range encompassed within the claims, which includes antibodies to HER2 which have not been characterized in terms of functionality and epitope recognition, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 26, 28, 37-43, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shepard HM *et al* (J. Clin. Immunol. 1991 May;11(3):117-127) in view of Draber *et al* (J. Immunol Methods 1995 Apr; (181(1):37-43), Sato *et al* (Cancer 1992 Nov; 70(10):2493-8), Nielsen AL *et al* (Am. J. Clin. Pathol. 1994 Jul;102(1):76-9), Natali *et al* (Int. J. Cancer 1990 ;45 457-461), Roy *et al* (Dev Biol Stand 1992 ;74 :323-39 ;discussion 340).

Claims 26, 28, 37-43, and 51 are drawn to a method of treating cancer comprising the administration of a formulation that comprises an antibody (4D5, also known as HERCEPTIN®) and a lyoprotectant, wherein the cancers are selected from endometrial cancer, lung cancer, bladder cancer, and ductal carcimona *in situ.*

Shepard *et al* teach that an antibody, 4D5, can inhibit cell growth when HER2 is overexpressed in a tumor cell, such as breast, ovarian, and lung carcinomas. Shepard *et al* further suggests that the antibody, 4D5, can be used for treating tumors that overexpress HER2 protooncogene. Shepard *et al* does not specifically teach or disclose HER2 expression in endometrial cancer, bladder cancer, colon cancer, or ductal carcinoma *in situ* and does not specifically disclose of a formulation wherein an antibody is lyophilized in the presence of lyoprotectants.

Nielsen *et al*, Sato *et al*, and Natali *et al* teach the expression of HER2 in endometrial cancer, bladder cancer, colon cancer and ductal carcinoma in situ, respectively.

Draber *et al* disclose a procedure that teaches the lyophilizing/freeze-drying of an antibody, wherein trehalose is used as a lyoprotectant, and show that such antibodies can be stored for a long time at ambient temperatures.

Roy *et al* teach that antibody formulations can contain glycine and mannitol as useful bulking agents in freeze-dried preparations of antibodies.

It would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art to treat cancer, especially, endometrial cancer, bladder cancer, colon cancer, lung cancer, or ductal carcinoma *in situ* by administering a formulation comprising an antibody, 4D5/Herceptin®, lyophilized in the presence of a lyoprotectants and bulking agents, because Sheppard *et al* teaches that the antibody 4D5 can be used as an agent for growth inhibition of tumor cells that overexpress HER2. Nielsen *et al*, Sato *et al.* and Natali *et al* teach that the expression HER2 is also

found in endometrial cancer, lung cancer, bladder cancer, colon cancer, and ductal carcinoma *in situ*, and Draber *et al* states that "freeze-drying of ...antibodies permits convenient long-term storage of large quantities of antibodies, facilitates their transport at ambient tempartures, and simplifies the construction of pre-aliquoted kits based on such antibodies". Although Draber *et al* does not specifically disclose the lyoprotectant:antibody ratio as claimed in the instant application, but in the absence of some evidence to the contrary, the recited molar ratios would be considered to be routine optimization of a known formulation. Roy *et al* teach the addition of glycine and mannitol to an antibody formulation during the freeze-drying procedure. One of ordinary skill would have had a reasonable expectation of success because Sheppard *et al* teaches that 4D5/HERCEPTIN® is effective in treating cancers that overexpress HER2. Furthermore, subcutaneous administration of the antibody formulation claimed in the instant application would have been obvious because these methods are commonly used in the administration of other compounds and agents to a patient.

Conclusion

No claim is allowed. Because new grounds of rejection were raised in the instant office action, this action is made **NON-FINAL.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
September 3, 2002

Brenda Brumback
BRENDA BRUMBACK
PATENT EXAMINER
Primary